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FDA/IVD Industry Overview

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IVD Initiatives and Directions

- FDA is continuing to reevaluate regulatory review processes, especially for medical devices
- In August 2010, OIVD staff characterized industry concerns that these initiatives might adversely impact OIVD activities and practices as “Hype vs. Reality”
- OIVD indicated that continued open communication, flexibility in regulatory applications, and a focus on sound science would be the norm, not the exception, despite regulatory process reevaluations

Regulatory Reality

- OIVD processes generally appear to be more interactive and open to industry feedback (compared to ODE), but FDA's global shift to heightened regulatory controls has had an impact
  - Voluntary recalls classified at highest level (class I) have increased significantly
  - Premarket clearances have declined slightly, with an increase in NSE decisions and no apparent increase in de novo downclassifications
  - PMA and PMA Supplements increasing

Regulatory Reality

- October to April reported class I recalls (by product) are higher for both OIVD and CDRH in total
  - October 2009 to April 2010 = 2 OIVD products in 131 total device recalls (< 2%)
  - October 2010 to April 2011 = 51 OIVD products in 319 total device recalls (≈ 16%)

Regulatory Reality

- Premarket notification clearances have declined slightly
  - October 2009 to April 2010 = 163 clearances with no de novo downclassifications
  - October 2010 to April 2011 = 145 clearances with 1 de novo downclassification
- Despite pre-IDE process as an aid to creating common understanding, clearance of new technologies and IVD improvements has remained relatively unchanged

Regulatory Reality

- Slight decline in number of clearances has coincided with an FDA reported* increase in NSE decisions
  - Overall NSE rate doubled from 4% in FY 2009 to 8% in FY 2010
  - SE rate dropped from 80% in FY 2009 to 73% in FY 2010
  - Industry perception has been that FDA may be meeting its MDUFA goals by issuing more NSEs

* FDA - Industry MDUFA III Reauthorization Meeting, March 7, 2011

Regulatory Reality

- PMA and PMA Supplement approvals for IVD products have *increased*
  - October 2009 to April 2010 = 71 approvals
  - October 2010 to April 2011 = 105 approvals
- Unclear whether increase is due to submission of supplements for modifications that would previously have been reported in Annual Reports

Regulatory Reality

- Heightened oversight extends to scientific thresholds in premarket review
  - September 2010 “Establishing the Performance Characteristics of In Vitro Diagnostic Devices for the Detection of *Helicobacter pylori*”
  - FDA states “Endoscopic biopsy …is considered the gold standard” for establishing IVD performance
  - But, AGA and clinicians recommend that patients avoid risks of biopsy unless it is clinically warranted (*e.g.,* continued symptoms)
    - Clinicians are unwilling to biopsy patients unless they are symptomatic
    - Subjects may elect to drop out of study if biopsy is required
    - IRBs may be unwilling to approve study design
    - Alternative comparators (breath tests, fecal antigen tests) exist
  - FDA approach may impact ability of new or modified tests to be studied effectively

Goals and Objectives

- FDA's stated regulatory goals include:
  - Flexibility – by developing "new regulatory frameworks" that address new products
  - Collaboration – by working with academia and industry "to identify knowledge gaps and fill them; identify confidence deficits and address them"
  - Openness – by being "more transparent and endeavor[ing] to help the public understand the rationale and reasoning behind the decisions we make which have such far-reaching impacts on public health."
- Overarching goals of the agency today continue to be guiding the approval process to ensure "a future that provides safer and more effective therapies"
- Industry perception is that there may be a disconnect between stated goals and current practices

Impact

- FDA's heightened focus and uneven application could lessen predictability of the regulatory requirements and may lengthen the premarket review process
- The pendulum appears to have swung back toward a zero risk mentality in all phases of premarket and postmarket review

IVD Initiatives and Directions

- Tensions between safety and transparency likely will continue to arise
  - Companies and consultants are reporting increased premarket review times for many IVD regulatory submissions
  - Reducing flexibility in 510(k) reviews has not led to an increase in de novo downclassifications
  - OIVD correspondence with clients on premarket reviews, CLIA Waiver decisions, and corrections/removals has been consistently more conclusory, with little or no “rationale” or “reasoning”

IVD Initiatives and Directions

- Significant areas likely to be impacted as we move forward include
  - Drug and device combinations, such as companion diagnostic tests
  - Laboratory developed tests and IVDMIAs
  - Areas previously viewed as outside the scope of FDA enforcement, such as workplace (nondiagnostic) drug testing
  - The premarket review process

Companion Diagnostics

- OIVD indicated before 2010 AMDM Annual Meeting that guidance is forthcoming
- Specific companion diagnostic tests and drugs historically have been approved through separate FDA pathways
  - Applies even when the diagnostics were developed concurrently with the therapeutic
- FDA has suggested, however, that
  - Companion diagnostics often may be combination products
  - The product's primary mode of action likely will be based on the drug component
  - Approach would likely require NDA or BLA approval, with the diagnostic test information included in the drug application

LDTs and IVDMIAs

- Lengthening FDA review times for IVDs encourages development of clinical laboratory services, if LDT approach is seen as a more flexible and faster pathway for bringing new healthcare technologies to patients
- FDA has been working with stakeholders to define how LDT and IVDMIA oversight can best be implemented
- FDA proposed in 2010 a risk-based oversight and sought stakeholder input on:
  - the potential benefits of increased FDA oversight of LDTs
  - suggested approaches of risk stratification of LDTs
  - specific challenges faced by clinical laboratories in meeting FDA regulations
  - how might increased oversight of LDTs affect diagnostic test innovation
- While FDA is developing an approach, companies and clinical laboratories must carefully assess when and how to launch LDTs versus IVDs

Workplace Drug Testing

- Drug testing of employees, such as SAMHSA testing programs
  - Traditionally viewed by workplace, SAMHSA, and CMS as non-diagnostic
  - Tested individuals not referred to treatment
  - Results not used for diagnosis
  - Characterized by CMS as "forensic" tests with regard to laboratory complexity categorization
  - FDA generally does not regulate forensic (defined by FDA as law enforcement) testing
- Recent OIVD statements indicate FDA concern that workplace drug tests should be regulated
  - Does FDA have authority?
    - Tests do not appear to be intended for diagnostic use
    - There is no direct impact on individual patient (*i.e.,* no diagnosis of disease or condition) and little to no public health impact
  - FDA has limited resources
  - Approach could open door to more extensive regulation of other "forensic" test areas

Premarket Review Pathways

- 510(k) Notices
  - Flexibility in assessing technologies helped introduce novel methods
    - Culture methods compared to DNA detection
    - ELISA methods compared to PCR
  - Flexibility in reviewing combined predicates helped introduce important diagnostic tools
- Heightened premarket thresholds may be contributing to increase in NSE decisions
  - Will OIVD recommit to the de novo downclassification process?
  - Will concerns lead to requests for expanded clinical studies and extensive additional data?

Looking Ahead

- Regulatory directions are always subject to change
- ASRs and LTDs will continue to be scrutinized using a risk based approach, but case-by-case regulation can create ambiguity
- MDUFMA will continue to impact FDA resources
- Review of increasingly complex IVDs and device technologies requires diversity in staff training and experience
  - Risk-based approach unchanged, but
  - Tolerance of recognized and “reasonable” risks to achieve public health benefits appears to be at a low
  - New technologies may raise new risks
  - Heightened scrutiny will impact review processes and new/modified product availability

FDA and Industry

- FDA regulatory initiatives relating to IVDs have been frequent, increasing in number, and may involve legislative and refocused regulatory initiatives
- Manufacturers, laboratories, and physicians should try to keep abreast of new developments
- Where possible, trade associations, professional associations, and interested parties should make their views known about the need to continue streamlining the IVD clearance/approval process
- Agency feedback and open communication a must

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